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Weekly fluctuation of intraocular pressure in exfoliation glaucoma : long-term follow-up with self-tonometry

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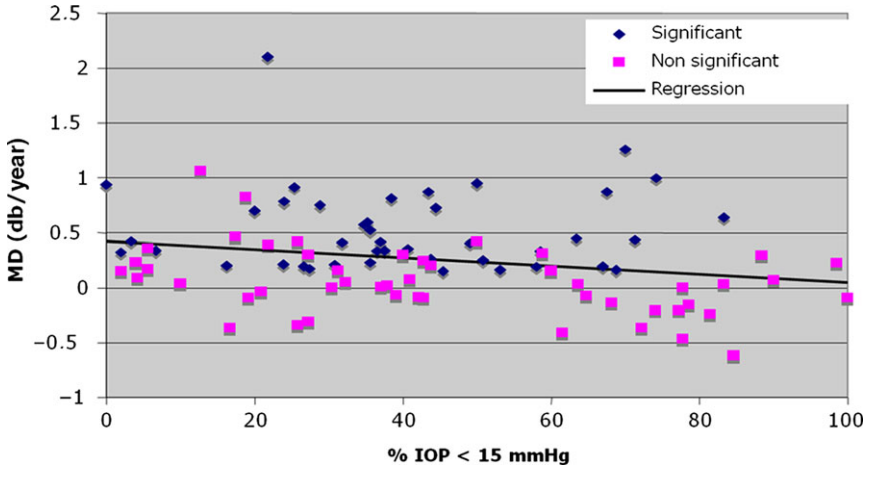

Fig. 1. Rate of progression of visual fields (n = 91 eyes) calculated by linear regression of mean defect (MD) over time. Each regression parameter with a significance level below or above 5% is indicated by a diamond or a triangle, respectively, and plotted against the number of visits with pressure measurements below 15 mmHg (regression coefficient 0.004 ± 0.002, r = 0.22, p = 0.04).

the chosen level divided by the total number of IOP times 100%. SPSS version 7.0 (IBM, Armonk, NY, USA) was used for the analysis.

Forty-six patients (91 eyes; mean follow-up time, 11 years) were included. The mean rate of MD progression was 0.26 dB/year. Sight-related quality of life (MD worse than 15 dB in both eyes (Peters et al. 2015)) would be affected in 41% of the patients (19 of 46) during the expected lifetime. The MD rate in eyes with significant visual field progression was 0.53 dB/year (46% of eyes). Comparing mean rates of MD progression with the fraction (%) of IOP measurements <16 and <15 mmHg showed a significant difference for < 15 mmHg (0.13 dB/year (31 eyes) versus 0.33 dB/year (60 eyes), p = 0.04)).

Comparing mean rates of MD progression with the fraction (%) of IOP measurements lower than 16 and 15 mmHg, respectively (Fig. 1), showed a significant difference for a discriminatory level of 15 mmHg. The rates of MD progression calculated by linear regression correlated significantly to the fraction of treated pressures that were lower than 15 mmHg (Fig. 1; r = −0.22; p = 0.04; Fig. 1).

In conclusion, the study shows that the mean rate of MD progression in patients with NTG was low (0.26 dB/year) but with a high interpatient variability. In comparison, the rate of MD progression in untreated NTG in whites has been shown to be 0.41 (Anderson et al. 2001) and 0.36 dB/year (Heijl et al. 2009) but with large interpatient variability in both studies like in this study. The rate of MD progression in whites with treated NTG has been shown to be 0.35 dB/year after 5 years (Ahrlich et al. 2010) and between 0.2 and 0.4 dB/year after 9 years (Anderson et al. 2003).

In this study, the rate of MD progression in the eyes with significant visual field progression was 0.53 dB/year (46% of the eyes). This is in accordance with the observation that only 34% of the eyes in this study have IOP measurements predominantly on or below the calculated target pressure (14 mmHg). Intensifying treatment in patients with progressive NTG in clinical care therefore seems advisable.

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Weekly fluctuation of intraocular pressure in exfoliation glaucoma: long-term follow-up with self-tonometry

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Editor,

Exfoliation glaucoma (XFG) is differentiated from primary open-angle glaucoma (POAG) by its clinical and histopathological features (Vesti & Kivelä 2000). Elevation of intraocular pressure (IOP) in EXG is associated with an increase in aqueous outflow resistance. It may be caused by endothelial dysfunction, exfoliation material, pigment liberation from the iris and ciliary epithelia, or a combination of these factors. At the time of diagnosis, IOP in EXG is higher than in POAG and shows more fluctuation (Konstas et al. 1997). The peak IOP occurs most frequently outside the office hours. A single measurement of

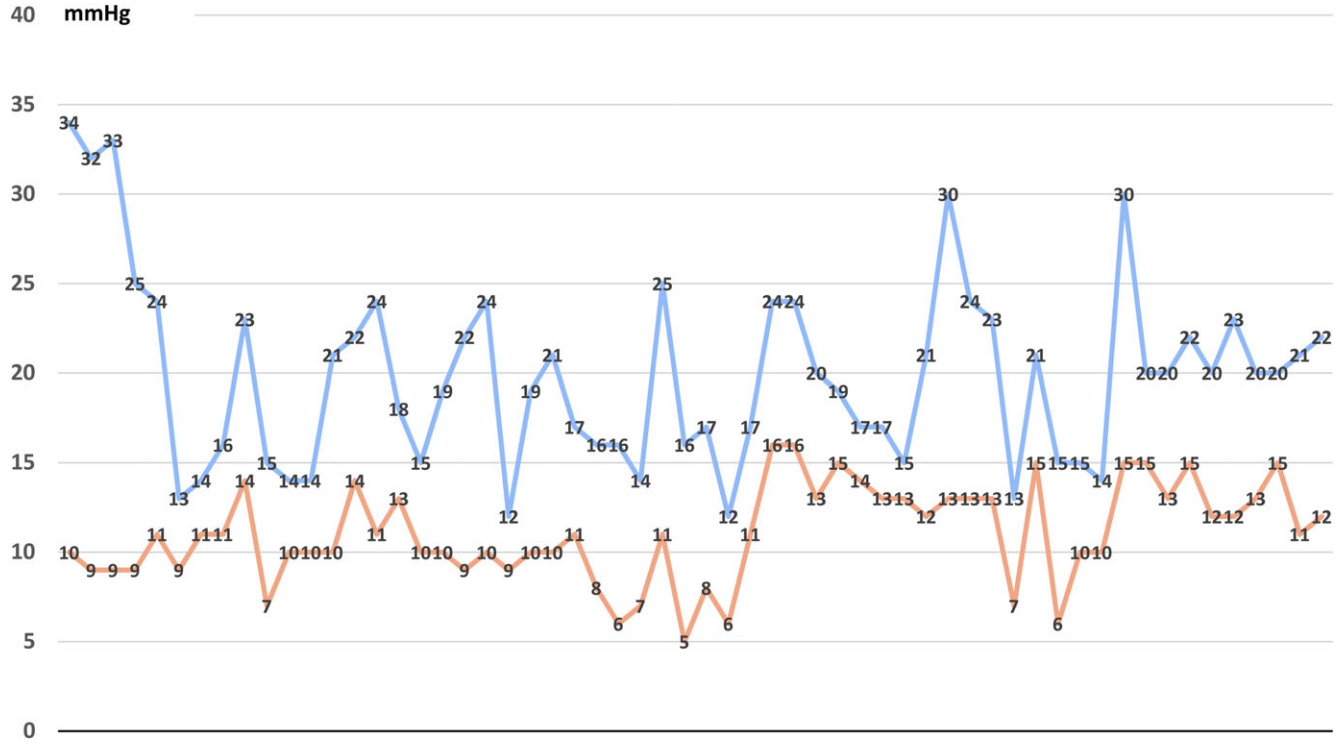

Fig. 1. Results of weekly self-tonometry performed on 60 days during a 12-month period. Lower line is the right eye, higher line the left eye.

the, typically with, Goldmann applanation tonometry (GAT) is not sufficient to estimate the average IOP level (Konstas et al. 1997). One way to solve this problem is to use of an electromagnetic rebound tonometer requiring no anaesthesia that has been found to be suitable for home and self-tonometry (Tarkkanen et al. 2010; Sakamoto et al. 2014;. In UK, 73% of glaucoma patients learned to use this method (Pronin et al. 2017). We have found that if the patient is well motivated, age is not an obstacle.

Our patient is an 84-year-old male with bilateral exfoliation diagnosed at the age of 69 years. Over the years, his IOP remained at lower teens. He underwent bilateral cataract surgery with intraocular lens implantation at the age of 80 years. His visual acuities, optic discs and visual fields were normal. Chamber angles were wide open but showed exfoliation deposits and pigmentation. Exfoliation material also was present at the pupillary border. Recently, the IOP measured on three different occasions using GAT was on average 14/36 mmHg. Although we detected no injury to the optic disc, if left untreated, he would be at risk of IOP-related complications, including central retinal vein occlusion. Hence, we prescribed preservation-free combination of bimatoprost and timolol once a day to the left eye. The target IOP was set at 20 mmHg or less. As he was interested in self-tonometry, he began to control his IOP at home once a week using iCare HOME rebound tonometer (iCare Finland, Helsinki, Finland). The metre stores each result but the patient cannot see the IOP. Initially, the senior author (AT) verified the accuracy of his measurements against GAT. He always measured the IOP several times a day and we recorded the highest reading. During 12 months, the IOP was controlled on 60 days. At the end of the project, no change in the left optic disc could be detected.

The IOP fluctuation was marked in both eyes (Fig. 1). In the right eye, the IOP varied between 5 and 16 mmHg, with a mean of 11 mmHg [standard deviation (SD), 2.7]. In the left eye, the fluctuation was more pronounced and the IOP varied between 12 and 33 mmHg with a mean of 20 (SD, 4.9) mmHg. The IOP exceeded the target IOP of 20 mmHg 22 times of 57 (38%).

Elevated IOP is the main and the only modifiable risk factor for optic nerve damage in glaucoma. Self-tonometry is useful in the diagnosis and therapy of especially those types of glaucoma with known tendency to high IOP and prominent fluctuation, such as EXG. Should there be progression of glaucomatous damage, the ophthalmologist can verify with confidence whether the target IOP is too high or whether the treatment is insufficient to maintain the IOP at the target level between office visits. We recommend self-tonometry for wider use in managing glaucoma.

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Considerations for ophthalmic applications of optogenetics

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Editor,

Optogenetics, or the use of light-sensitive proteins to observe and control events in living cells, is considered one of the most groundbreaking innovations in neuroscience in recent years. By bestowing light sensitivity to retinal cells typically downstream of retinal damage/dysfunction, optogenetics has the potential to treat many diseases regardless of patient-specific mutations. This is a major advantage when (1) the mutation is unknown, (2) gene replacement has not yet proven feasible and (3) retinal neurons and supporting cells have undergone significant anatomical and functional remodelling.

Despite several strengths with applications being explored in clinical trials, the use of optogenetics in ophthalmology prompts several considerations. Principally, most nonmodified microbial opsins used for ophthalmic applications require intense light for activation (between 10^{14} and 10^{17} photons/cm^2/s). For example, blue light stimulation required by the most applied opsin (Channelrhodopsin-2) may variably exceed the safety threshold of artificial radiation for the human retina (International Commission on Non-Ionizing Radiation Protection 2013). Intense light stimulation is required for two reasons: (1) the relatively low expression level of opsins in transduced retina when compared to native visual pigment (due to toxic and immunologic concerns) as well as (2) the relatively weak signal generation of microbial ion channels or pumps (typically type 1 opsins) when compared to the G-protein coupled signal amplification of human rhodopsin (type 2 opsins).

One approach to overcome the reliance on potentially damaging wavelengths of light is the creation of modified red-shifted opsins (Douar et al. 2016) allowing for activation at safer spectra. Another approach is the creation of photopharmacologic and optogenetic actuators with higher sensitivities. For example, engineered chemical photoswitches that bestow light sensitivity to endogenous transmembrane channels can be activated at 4×10^{13} photons/cm^2/s. It is also possible engineer and/or apply more efficient opsins such as the modified human melanopsin (opto-mGluR6) conferring light sensitivity to retinal ganglion cells (RGCs) at 6×10^{12} photons/cm^2/s (van Wyk et al. 2015) and human rod opsin conferring light sensitivity to retinal bipolar cells at 10^{12} photons/cm^2/s.(Kapetanovic et al. 2017) An additional tool is to employ light-projecting goggles to capture the visual scene, amplify the light intensity of various features and project the image onto the retina at wavelengths optimized for opsin activation.(Goetz et al. 2013) Such goggles may also preserve the loss of meaningful visual mapping when nonphotoreceptor elements (bipolar cells or RGCs) generate the light-transduction signalling cascade. This is accomplished by projecting light in spatiotemporally altered patterns meaningful to various subpopulations of RGCs.

Further limitations implicit in current optogenetic approaches are those pertaining to viral-based gene therapy. Briefly, these include the variable efficiency of viral transduction, non-specific opsin expression and off-target viral effects due to leaky promoters, the stability of expression with the potential for cellular toxicity due to gene product buildup and others. However, significant advancements have been made in viral-based gene therapy including the first FDA approved gene therapy (for Leber's congenital amaurosis) on 12/19/2017.

A significant hurdle to the long-term efficacy of optogenetics yet to be addressed is retinal remodelling. This occurs in chronic dystrophic and degenerative diseases where the structure and function of remaining neuronal signalling pathways are disrupted. Even when prior considerations are addressed, targeting neurons that are mis-wired and/or functionally damaged limits meaningful visual gains. Retinal remodelling remains an issue of concern for all genetic, prosthetic and/or regenerative therapies for the retina and will need to be investigated further as a field.

Optogenetics remains a remarkable neuroscientific tool with incredible promise for ophthalmology. This letter is not intended to discourage the use of optogenetics in a clinical setting, but rather to illuminate surmountable hurdles and to raise awareness for designing the next generation of ophthalmic optogenetic tools.

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